HHS Public Access

Author manuscript

Curr Pharm Biotechnol. Author manuscript; available in PMC 2015 August 18.

Published in final edited form as:

Curr Pharm Biotechnol. 2012 August ; 13(10): 1914–1916.

Antidotes and Rescue Therapies

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In this issue of *Current Pharmaceutical Biotechnology*, we present a series of articles on the clinical use of antidotes and rescue therapies. Our goal is to heighten awareness in the scientific community about the benefits of and challenges to research and development for these agents. The intention is to stimulate further interest in this area, leading to new and improved antidotes. Antidotes are medications that limit the progression of adverse health outcomes that result from exposure to exogenous agents: drugs, metals, and toxins. Antidotes are commonly used to treat poisoned patients and, in select situations, patients receiving chemotherapy.

The use of antidotes depends on the clinical indication and the availability of the product. The National Poison Data System (NPDS) reports the annual occurrence use of selected antidotes and rescue therapies available for poisoned patients [1]. These reports, compiled from calls made by the public to Poison Control Centers throughout the United States, likely under represent the actual figures because calls are made on a voluntary basis. Since the 2004 Food and Drug Administration (FDA) approval of the intravenous formulation of N-acetylcysteine (IV NAC) for human acetaminophen poisonings in the United States, annual use of IV NAC increased by approximately 13 fold. Average annual use during 1999–2003 was 1,279; in 2009, the number was 16,260 [1–11]. Similarly, the use of fomepizole (4-methyl pyrazole) for ethylene glycol and methanol poisonings increased from 305 in 2000 to 1,743 in 2009 [1, 3–11]. Fomepizole was FDA approved for use in patients poisoned with ethylene glycol in 1997 and methanol in 2000. Prior to the availability of fomepizole, ethanol was used to treat these patients. Its annual use decreased from 576 during 1992 to 1996 to 96 in 2009—largely because of its unfavorable safety and efficacy profiles compared to fomepizole [1–19]. These examples indicate the clinical need for antidotes and the demand for antidotes when they become available.

Antidotes improve health outcomes in poisoned patients by reducing overall morbidity and mortality. In a multicenter clinical trial consisting of 150 patients with digitalis toxicity, use of digoxin-specific antibody fragments resulted in accelerated recovery and 54% decreased

DISCLOSURE

Opinions expressed in this paper are those of the authors and do not necessarily reflect the official position of the Centers for Disease Control and Prevention.

mortality in poisoned patients [20]. The improved clinical response of patients with digitalis toxicity from digoxin antibody therapy was observed in 86% [21] and 90% [20] of patients participating in two large multicenter studies. An inadequate dose of digoxin antibody was associated with an incomplete clinical response [21]. In a predictive model, the use of digoxin antibody reduced the length of hospital stay (LOS) by 1.5 days (LOS was 1.5 days with digoxin antibody therapy and 3.0 days without it), decreased cost in 37% of cases, and reduced LOS in 72% of cases compared to standard therapy without digoxin antibody in patients with non-life-threatening digoxin toxicity [22].

In patients with acetaminophen poisoning, N-acetylcysteine (NAC) administered within 8 hours of acetaminophen ingestion decreased the percent of patients with hepatotoxicity [23, 24] and improved survival in patients with fulminant hepatic failure (FHF) [25]. In a multicenter prospective randomized study, 11/110 patients treated with NAC at greater than 8 hours of ingestion developed hepatotoxicity, in comparison to 0/57 patients treated within 8 hours ($p=0.0135$) [24]. In a prospective randomized controlled trial of patients with FHF from acetaminophen toxicity, patients receiving prolonged NAC treatment had lower incidences of cerebral edema and hypotension requiring intravenous inotropic support, likely contributing to a higher rate of survival than patients not treated with NAC (48% vs. 20%, $p=0.037$, 95% confidence interval for difference in proportions surviving 3% to 53%) [25].

Although poisoned patients are the common focus of antidotes, cancer patients receiving chemotherapy can benefit from these agents as well. In randomized controlled trials, dexraxozane reduced the incidence of doxorubicin-induced cardiac dysfunction (left ventricular ejection fraction) and congestive heart failure in patients treated for metastatic breast cancer [26, 27]. Dexrazoxane is approved by FDA for use in patients receiving $>300 mg/m^2$ of doxorubicin to reduce the risk for cardiac toxicity [28].

Antivenoms to species of the black widow spider (*Lactrodectus*) and pit viper snakes found in the United States (*Crotalus*, *Sistrurus*, and *Agkistrodon*) also have demonstrated clinical efficacy in envenomated patients. In a retrospective study of 118 patients with black widow spider envenomations, patients treated with the antivenom improved sooner based on the duration of their symptoms (mean of 9 hours vs. 22 hours, $p<0.05$) and had a lower percent of hospitalization (12% vs. 52%, $p<0.05$) than patients not treated with the antivenom [29]. Pit viper antivenom, available in the United States for several years, has been shown to be effective in the treatment of patients with coagulopathies from envenomations. The immunoglobulin G (IgG) formulation was associated with significant allergic reactions, but the newer version of pit viper antivenom contains only the antigen-binding fragment (Fab fragment) and has a lower incidence and severity of allergic reactions (5.4–19% vs. 23–56%) than the IgG formulation [30]. However, the recurrence of toxicity with the Fab formulation is a recognized concern because of the greater clearance of the antivenom than the venom from the body. The pit viper antivenom, fomepizole, and hydroxycobalamin (for cyanide poisoning) are examples of opportunities for the development of antidotes with enhanced safety profiles.

Other opportunities for research and development of antidotes include their use in populations of concern (e.g., children), selected settings (e.g., mass casualties), and new

approaches (e.g., aptamers-antidote pairs). Although randomized controlled trials are the desired study design, they can be difficult for agents that have been in use for many years because of ethical concerns. Silibinin (for amatoxin poisoning); reactive skin decontamination lotion (for chemical warfare agents); hydroxycobalamin, calcium and zinc salts of diethylenetriaminepentaacetate (for chelation of internal contamination with plutonium, americium, curium); and oligonucleotide antidotes for antithrombotic agents are such examples, reviewed in this issue of the *Current Pharmaceutical Biotechnology*.

We would like to express our appreciation of the impressive efforts of the contributing authors to this issue of the *Current Pharmaceutical Biotechnology*. We hope the readers will take away from the articles some newfound information that enables them to further their own activities that can lead to enhanced antidotes and rescue therapies in the future. The success of this effort will require a collaborative effort from various sectors involved with this focus. Although antidotes can limit the mortality and morbidity of poisoned patients, prevention remains the best therapy.

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